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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/894,246	05/22/98	PERRICAUDET M	EX95001-US

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EXAMINER	
CHEN,S	
ART UNIT	**PAPER NUMBER**
1633	16

DATE MAILED: 12/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/894,246	Perricaudet et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☒ Responsive to communication(s) filed on *Aug 24, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *26-64* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *26-64* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *15*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed 8-24-00 has been entered. Claims 26, 29, 30, 40, 43, 47 and 48 have been amended. Claims 57-64 have been added. Claims 26-64 are pending.

Claim Objections

Claim 40 is objected because the claim was indicated to be **amended** but it is unclear what is amended.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 61-64 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps are: for example, whether the gene of interest is expressed in the cell *in vitro* or *in vivo*, and whether the survival of the cell has been prolonged.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 26-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination of anti-CD4 antibody and Ad-βgal-gp19K, does not reasonably provide enablement for a composition comprising any immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and any immunoprotective gene such as ICP47 gene and UL18 gene, and a method for expression of a therapeutic gene using said composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 26-60 are directed to a composition comprising an immunosuppressive agent and a recombinant adenovirus expressing a gene including a therapeutic gene and an immunoprotective gene (e.g. gp19K) and a method for expression of said gene including a therapeutic gene comprising consecutively or simultaneously administering said immunosuppressive agent (e.g. CTLA4Ig) and said recombinant adenovirus into a subject. Claims 61-64 are directed to a method of prolonging the survival of a cell expressing a gene of

interest comprising administering the recombinant adenovirus set forth above to a cell of an animal and treating the animal with an immunosuppressive agent.

Claims 26-64 encompass any immunoprotective gene, or the combination of immunoprotective genes, including various virus genes and the known and yet to be identified genes whose products act on the activity of a major histocompatibility complex (MHC) or on the activity of a cytokine etc. The specification of the present application only discloses decreasing CD4+, CD3+ and CD8+ T cells by the combination of anti-CD3 or anti-CD4 antibody with Ad-βgal-gp19K expressing gp19K protein of adenovirus, and decreasing cytotoxic activity of splenocytes, isolated from animals treated with anti-CD4 antibody and Ad-βgal-gp19K, on p815-β-gal target cells expressing β-galactosidase, and prolonging the expression of β-gal in a liver of a mouse with the combination of anti-CD4 antibody and Ad-βgal-gp19K.

The claims read on gene therapy in light of the specification which indicates that the present application is to provide a novel method for prolonging gene, e.g. therapeutic gene, expression in a gene therapy using adenovirus vector *in vivo*. B-gal was known in the art at the time of the invention as a marker gene rather than a therapeutic gene. The specification of the present application fails to provide adequate guidance and evidence that an adenovirus vector as claimed in the present application expressing any therapeutic gene and immunoprotective gene as separate proteins or as a fusion protein in combination with an immunosuppressive agent could provide therapeutic effects for a gene therapy in a subject *in vivo*. The specification also fails to provide adequate guidance and evidence for the correlation of a specific therapeutic gene with a

particular disease or disorder such that the administration of the adenovirus expressing said therapeutic gene would provide therapeutic effects for a gene therapy in a subject *in vivo*.

The state of the prior art for gene therapy was not well developed and was highly unpredictable at the time of the invention. Verma et al., 1997 (W) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al., 1996 (X) explains that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important factors for successful gene transfer *in vivo*. These factors differ dramatically based on the vector used, and the disease being treated (e.g. bridging pages 81-82). Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and to obtain sustained expression (see Verma et al., page 239, col. 3).

In addition, the amendment filed 12-13-99 indicates that the prolonged expression of β-gal as disclosed in the specification with the combination of immunosuppressive agent and adenovirus expressing β-gal and the **immunoprotective gene** gp-19 was surprised and unexpected (section (f)). The specification of the present application also indicates that "this immune response against infected cells varies according to the nature of the organ which sustains

the injection and according to the method of injection which is employed. Therefore, it was unpredictable at the time of the invention whether any immunoprotective gene other than the adenovirus gp-19 gene could obtain sufficient expression *in vivo* and **unexpectedly** prolong the expression of gene of interest, such as a therapeutic gene, *in vivo* such as to provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder. Further, claim 26 has the open language "comprising" which reads on more than one immunoprotective genes in the claimed invention. Since it was unpredictable at the time of the invention whether any immunoprotective gene other than the adenovirus gp-19 gene could obtain sufficient expression *in vivo* and **unexpectedly** prolong the expression of gene of interest, such as a therapeutic gene, *in vivo* such as to provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder, it was also unpredictable whether more than one immunoprotective genes would result in similar effect as one immunoprotective gene. It is unclear what the specific mechanism of the interaction of two or more immunoprotective gene products in provding immunoprotective effects *in vivo*. It is also unclear whether the immunoprotective gene products would interact synergistically or counteract to each other such that none or decreased immunoprotective effect is obtained. The specification of the present application fails to provide adequate guidance for the mechanism of the interaction of more than one immunoprotective gene products that results in immunoprotective effect *in vivo* or for the mechanism of interaction of the immunoprotective gene product and therapeutic gene product *in vivo* such as to provide immunoprotective effects

and to provide **unexpectedly** prolonged expression of the therapeutic gene *in vivo* so as to achieve therapeutic effect in a subject for a gene therapy of a particular disease or disorder.

The expression of an immunoprotective gene *in vivo* depends on the administration route of the adenovirus vector, the targeted site, *in vivo* consequences of altered gene expression, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, and the stability of the mRNA. The specification of the present application fails to provide adequate guidance for a sufficient expression of any immunoprotective gene other than the adenovirus gp-19 gene *in vivo* such as to **unexpectedly** prolong the expression of gene of interest, such as a therapeutic gene, in the targeted cells and to provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder. It is unclear whether any immunoprotective gene other than the adenovirus gp-19 gene would **unexpectedly** prolong the expression of gene of interest, such as a therapeutic gene, in the targeted cells *in vivo* and provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder.

The specification only discloses the prolonged expression of β-gal in the liver of a mouse but fails to provide adequate guidance and evidence for the prolonged expression of any therapeutic gene in organs other than liver in a subject *in vivo*. Different organs, tissues or targeted site could vary physically and biologically such that the expression of a gene *in vivo* also could vary depending on the site being targeted. It is unclear whether the same immunoprotective gene could obtain sufficient expression in a particular organ, tissue or targeted

site such as to achieve prolonged expression of a gene of interest, such as a therapeutic gene, to provide therapeutic effect in a subject for a gene therapy of a particular disease or disorder.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention to engage in undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that Poller reference confirms the applicability of using the E3 region genes of adenovirus as an immunoprotective gene and "PTO provides no reasons to limit the applicability of the statements in the specification to only the exemplified immunosuppressive agents and immunoprotective genes". Applicants further argue that the specification only need to provide the prolonging expression of the gene introduced by the recombinant adenovirus and no further demonstration of "effectiveness" is required. This is not found persuasive because of the reasons set forth above and the reasons that Poller uses **E3 region genes** rather than **a single immuinoprotective gene**, and the adenoviral vector was targeted to **liver** and the expression of factor IX was detected in the plasma (e.g. p. 16). Poller presents a speccific combination of E3 region genes for providing immunoprotective effects. However, the specification of the present application fails to provide specific combination of immunoprotective genes in the E3 region of adenovirus or any other potential immunoprotective genes for providing immunoprotective effects *in vivo*. It is not clear whether a single gene in the E3 region other than the gp-19 gene or

combination of two or more immunoprotective genes could also provide prolonged expression of a gene of interest in a liver or any other organ, tissue or targeted site in a subject *in vivo*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

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